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Translational oncology toward benefiting cancer patients: the Sun Yat-sen University Cancer Center experience

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Cancer is a leading cause of death in China with an estimation of nearly 2 million deaths every year (Chen and Fu, 2011b). Matter of a public health importance in China and worldwide, the scientific community is still facing many obstacles to eradicate cancer: complexity of a multi-factorial disease with organ-based specificities, high failure rate of many anti-cancer drugs in clinical trials, lack of understanding of the cancer genesis factors... Among all the possibility for new therapies, what should be the next trends for cancer treatment? Dr. Yixin Zeng, president of SYSUCC, emphasized that molecular typing and personalized therapy is the future direction of modern medicine, and may eventually lead to a cure for cancer. Indeed, the field of oncology is moving toward the development of individualized treatment based on tumor molecular profiling.

Sun Yat-sen University Cancer Center (SYSUCC) is the largest integrated center in southern China for cancer-related care, education, research, and prevention. In addition with a comprehensive range of health-care services for cancer diagnosis and treatment (capacity over 1000 beds), SYSUCC has the necessary multi-disciplinary platform to conduct translational research with a SFDA accredited Clinical Trial Center, the State Key Laboratory of Oncology in South China and a tumor biobank.

As mentioned by Minister Zhu Chen and Dr. Guangbiao Zhou in a previous issue of *Science China*, translational medicine is a people oriented practice (Chen et al., 2011b), defined as a bi-directional science aiming either to translate basic science discoveries into clinical applications (often referred as bench to bedside) or to convert clinical observations into mechanism studies (bedside to bench). In this review, we propose to summarize all translational studies from SYSUCC that promises to benefit patients.

LARGE PANEL OF TRANSLATIONAL STUDIES ON NASOPHARYNGEAL CARCINOMA

Nasopharyngeal carcinoma, a challenging disease

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma originating from the epithelial cell of the nasopharynx. NPC has a very unbalanced epidemiologic repartition; although very frequent in South China and Southeast Asia, where its incidence can reach 20–50 per 100000 in high endemic region, it is quite rare among the caucasian population (less than 1 per 100000 persons) (Lu et al., 2010; Cao et al., 2011; Adham et al., 2012; Kataki et al., 2011). This disease is thus extensively researched in SYSUCC, where every year about 2500 new NPC patients are treated.

NPC is a highly malignant cancer that often invades adjacent regions and metastasizes to regional lymph nodes and distant organs. The overall five-year survival rate of NPC is

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around 60%, whereas the stage-specific five-year survival rates range from 88% at the early stage down to 28% at the advanced stage. Because symptoms related to NPC in the early stage are usually nonspecific, 80% of NPC patients have developed a late-stage tumor by the time of diagnosis. Therefore, it is important to acquire a basic understanding of the underlying genetic and molecular mechanisms of NPC's pathogenesis to explore the possible high-risk factors and identify the markers for susceptibility and early diagnosis of NPC.

Identification of genetic susceptibility and development of risk prediction model for nasopharyngeal carcinoma

The involvement of genetic susceptibility in the etiology of NPC provides a way toward NPC risk prediction (Simons, 2011; Shugart et al., 2011). Over the last decade, Dr. Yixin Zeng (president of SYSUCC) and his team have been working on the identification of genetic lesions that contribute to the development of NPC. From studies of high-risk NPC families, Dr. Zeng's team discovered a susceptibility locus in the 14.21-cM region of 4p15.1-q12 that was related to familial NPC (Feng et al., 2002). Moreover, based on a large-scale genome-wide analysis study, they have recently identified three novel loci for sporadic NPC, including MECOM on chromosome 3, CDKN2A/2B on chromosome 9, and TNFRSF19 on chromosome 13 (Bei et al., 2010). In addition, they found that DNA repair gene variants were associated with the risk of NPC in the Cantonese population of southern China (Qin et al., 2011). The identification of genetic risk factors for NPC is significant in developing an NPC risk prediction model and subsequent screening of the high-risk population to improve early diagnosis of NPC patients.

To establish an NPC risk prediction model, Dr. Zeng's ongoing research is separated into two parts: (i) identifying other genetic lesions that might lead to NPC (which will provide information relating to the genotype) and determining the sequence information from large samples of NPC patients and controls; and (ii) exploring the contribution of environmental factors, such as alcohol consumption and smoking as well as infection by Epstein-Barr virus, and the interaction of these factors with genetic lesions.

Using chip technology, the presence of genetic risk variants for one individual can be determined, and this simultaneously allows the detection of any genetic lesions that may be present. The genetic information can then be fed into a risk prediction model together with data relating to environmental risk exposure and virus infection; the result is a score that indicates an individual's risk of developing NPC. A person with a high risk score can then be advised to take further medical examination. Therefore, the accuracy of the prediction model that Dr. Zeng's team is currently working on will help people become more aware of the risk of NPC and will also increase the chances of early diagnosis.

Biomarkers and nasopharyngeal carcinoma prognosis

There is a pressing need to expand our knowledge about cancer biomarkers and develop a rapid, effective molecular classification platform to help diagnose NPC, identify the adapted treatment and predict clinical outcome. From the general opinion in SYSUCC, the current TNM staging system of NPC should be refined to have a better correlation between each stage and its associated prognosis. With the recent advances in molecular biology, scientists hope to find new molecular markers that can complement the existing staging system and improve treatment strategy for NPC.

Scientists in SYSUC are investigating this issue from different approaches and discovered several potential prognostic biomarkers for NPC. For example, Dr. Jianyong Shao and his team (Department of Molecular Diagnostics, SKL of Oncology in South China) developed a bioinformatics method to construct a prognosis classification system for NPC, called the NPC-support vector machine (SVM) classifier (Wang et al., 2011). With eight parameters (gender and protein level expression of seven genes), the classifier can separate NPC patients into two categories: high and low risks groups based on their five-year disease specific survival. This model aims to be applied in clinical practice and enhance individualized management of this disease.

Another study led by Dr. Jun Ma emphasizes the important role of MicroRNAs (miRNAs) for NPC prognosis. Indeed, miRNAs, a family of small non-coding RNAs, are known to be deregulated in many cancers and to be involved in the pathogenesis of NPC. Based on this, Dr. Jun Ma and his team proposed a five-miRNA signature, predictive of patient survival, which can potentially identify candidates for aggressive therapy (Liu et al., 2012).

NPC is known to be related to Epstein-Barr virus (EBV) infection and EBV-specific antibodies are routinely used for NPC diagnosis (Dardari et al., 2001) but not for prognosis. In Dr. Qiang Liu's study, researchers found that serological anti-enzyme rate (AER) of EBV DNase-specific neutralizing antibody could be used as an independent NPC prognostic marker complementing TNM staging (Xu et al., 2010).

ANTICANCER DRUG DEVELOPMENT

Molecular targeted therapy

In anti-cancer drug discovery, the model has shifted from non-specific cytotoxic chemotherapeutics to molecular targeted agents. Thanks to the progress of molecular biology, scientists are able to find small molecules that interfere with specific molecular pathways in cancer cells development to

inhibit their progression (Liu et al., 2011). Studies conducted at SYSUCC aim to identify and evaluate potential targets for treatment, especially for NPC and liver cancer.

Researchers have discovered that Met overexpression and PI3KCA mutation are common in NPC, which makes the PI3K/AKT pathway a potential target for treatment. For example, a recent study showed that DC120, a 2-pyrimidyl-5-amidothiazole compound, was inhibiting proliferation in human nasopharyngeal carcinoma and breast cancer cells (Deng et al., 2012). Interestingly, several other compounds targeting PI3K/AKT pathway were developed from natural products used in traditional Chinese medicine and showed *in-vitro* and *in-vivo* potent anti-cancer activities. For example, excisaninA from Isodon specifically induces tumor cell apoptosis and reduces tumor growth for hepatocellular carcinoma and breast cancer (Deng et al., 2009), SYUNZ-16 from *Arnebia euchroma* roots inhibits proliferation of lung adenocarcinoma and hepatocellular carcinoma (Deng et al., 2010) or emodin AMAD (azide methyl anthraquinone derivative) extracted from nature's giant knotweed rhizome showing promises for the treatment of Her2/neu-overexpressing cancers (Yan et al., 2011).

From a collaborative work with Sun Yat-sen University, School of Pharmaceutical Science, it was found that quinoline derivatives interacted preferentially with intramolecular G-quadruplex structures and were novel potent telomerase inhibitors (Zhou et al., 2006).

For many years, Dr. Liwu Fu and his group have been working on reversing multidrug resistance (MDR), a mechanism by which cancer cells tend to become resistant to chemotherapy. Tyrosine-kinase inhibitors are a hot area in anti-cancer drug development because they inhibit the function of ATP binding cassette transporters and restore the sensitivity of MDR cells (Chen et al., 2011a). For example, FG020326, a newly synthesized triaryl-substituted imidazole derivative, reversed MDR *in vitro* and *in vivo* (Dai et al., 2008a). Uncovering the anti-cancer properties of small molecules Apatinib and Lapatinib in combination with conventional chemotherapy is also an active and promising area of research at SYSUCC (Mi et al., 2010; Dai et al., 2008b)

Innovative antiangiogenesis agent against solid tumors —adenovirus carrying human endostatin (E10A)

Despite recent progress in the management of cancer, the majority of advanced metastatic solid tumors are still not curable using current treatment modalities. There are many reasons for the inability to eradicate malignant neoplasms using conventional cytotoxic drugs. Chemotherapy is not specific for cancer: it targets all rapidly proliferating cells by inhibiting DNA synthesis or interfering with different pathways of cell division and metabolism. Chemotherapy is frequently associated with significant dose-limiting side effects related to toxicity to normally dividing cells in the bone marrow, skin, and gastrointestinal mucosa. Developing a targeted anticancer drug is clearly beneficial to patients. Angiogenesis plays a critical role in cancer development and metastasis, and endostatin is one of the most effective inhibitors of angiogenesis.

An adenovirus-carrying endostatin gene product (E10A) has been developed at SYSUCC by Dr. Wenlin Huang, in conjunction with Guangzhou Doublle Bio-products Co., Ltd. (Guangzhou, China) for advanced head and neck tumors (Li et al., 2008; Lin et al., 2007; Huang et al., 2007). E10A, an adenovirus-carrying endostatin gene, can dramatically increase the tumor drug concentration in metronomic chemotherapy with low-dose cisplatin in a xenograft mouse model for head and neck squamous cell carcinoma. The formulation of the E10A product with a PEGylated and lyophilized preparation can be given as a venous injection. To investigate the effect of this new targeted drug, a multicenter phase II clinical trial has been conducted, and the results with progress-free survival rate are promising. The phase III clinical trial of E10A is on-going this year. Intellectual properties related to the formulation are covered by a Chinese patent, which has won the 12th China Patent Gold Award for innovative patents.

ESSENTIAL ROLE OF THE ANIMAL FACILITY FOR TRANSLATIONAL STUDIES

Animal models play a critical role to translate basic research discovery into clinical applications and, vice versa. In cancer research, animal models have been widely used for multiple purposes, including etiology studies, drug screening, cancer progression (tumorigenesis, metastasis, tumor angiogenesis, cachexia, etc.) and cancer prevention studies. The advantage of disease model based on animals over cell lines is that it mimics better human response to therapeutic in terms of physiological environment, genetic and morphologic features.

Aurora-A (Aur-A), a kinase involved in chromosome segregation during mitosis, has been reported to be a potential target for cancer therapy (Gautschi et al., 2008). Several studies, led by Dr. Qiang Liu, already proved the important role of Aur-A in diverse tumor characteristics *in vitro*. For example, Aur-A increases migration and reduces radiosensitivity in laryngeal cancer cells (Guan et al., 2007), and it also promotes epithelial-mesenchymal transition and invasiveness in nasopharyngeal carcinoma (Wan et al., 2008). So far, nude mice studies have shown that Aur-A promoted breast cancer migration and metastasis through the Collin-F-actin pathway (Wang et al., 2010). In order to test the efficiency of Aur-A targeted therapy, further *in vivo* studies are necessary, so, in that perspective, SYSUCC scientists are currently working on generating Aur-A inducible transgenic mice.

Other studies aim to identify the role of signal transducer

and activator of transcription-5 (STAT5) in leukemia using conditional knockout mouse. Leukemia phenotype can be induced by collecting bone marrow cells after Poly-IC treatment and infecting the cells with BCR/Abl or Flt3 virus. By analyzing bone marrow cells from wild type mice, scientists plan to have a better understanding of the STAT5 pathway involved in Leukemia development and thus find inhibitors for targeted therapy.

BIOBANK AS THE BASIS FOR TRANSLATIONAL STUDIES

Biobanks are essential for translational medical studies and are a valuable resource for both basic and clinical research. As one of the earliest (2001) and largest bio-repositories in China, the tumor biobank has become an important part of SYSUCC and the SKL of oncology in South China. Following the heterogeneity of cancer, large-sized biobanks are crucial to study the many aspects of this complex disease (Watson et al., 2010). SYSUCC biobank currently has nearly 15000 tissue samples and over 50000 blood samples collected from diagnosed patient for various tumors at different stages, including NPC and esophageal, lung, breast, stomach, colorectal, liver, head and neck, gynecologic and urinary cancers and lymphomas. In addition with a large number of samples, the biobank has been directly connected to the Hospital Information System (HIS), allowing an easy link between samples and their associated clinical data.

The rapid development of translational medicine urgently needs high-quality bio-specimens which is why SYSUCC continually introduce the latest national and international advances for standard management and quality control of the biobank. For example, the safety of bio-specimens stored in ultra-low temperature environment is ensured by a temperature management and remote alarm system. A management software was developed for sample information storage so that each sample can be found easily. More importantly, the biobank is equipped with two automated liquid workstations, an automated blood fractionation system and a nucleic extraction purification system. This advanced platform contributes to further maintain standard operation procedures to keep providing scientists with high quality biological samples.

Upon its establishment, SYSUCC tumor biobank actively participated in nearly 500 high level research projects. In addition with the genome-wide association study of nasopharyngeal carcinoma, the biobank contributed to several other large scale projects, such as studies of esophageal squamous-cell carcinoma collaborating with researchers from Chinese Academy of Medical Sciences and Peking Union Medical College, and studies of hepatic carcinoma collaborating with researchers from the State Key Laboratory of Proteomics.

In the past, SYSUCC has benefited from collaborations with tumor banks of other institutions such as Tianjin Medical University or the Fourth Military Medical University but such partnership needs a lot of technical and logistical coordination. To facilitate large-scale studies requiring an important number of various samples, the creation of national tumor biobanks in China seems mandatory. The American National Cancer Institute set up the first national human biobank in 2009, and it was named by *Time* as one of "10 Ideas That Will Change the World" in 2009. An internet shared network with other tumor biobanks is currently under development which will result in promoting the exchange of information among different researchers and accelerating the translation of discoveries from bench to beside, thus benefiting patients.

INVESTIGATING CLINICAL ISSUES USING BASIC RESEARCH APPROACHES AND DISEASE MODELS

Investigating cancer metastasis

The major obstacle in improving cancer treatment outcomes for many malignancies is metastasis. Metastatic cancer lesions are usually difficult to treat not only because they often involve multiple organs, but also because they are more likely to develop resistance to therapies through still-unknown mechanisms. Predicting and preventing metastasis is crucial in prolonging the survival time of cancer patients.

One ongoing effort at SYSUCC led by Dr. Chaonan Qian is investigating the mechanisms that underlie the motility of cancer cells (the "seeds") as well as the microenvironment in the lymph nodes (the "soil") that favors the growth of metastatic cells. The studies on the seeds have been sponsored by two grants from the National Natural Science Foundation of China, and they focus on the metastatic mechanism in NPC, which has the highest metastasis rate among head and neck cancers. The sentinel lymph node metastasis model developed by Dr. Qian's group can better represent the most frequent type of cancer spread in clinical scenarios. They have also isolated high- and low-metastasis cellular clones from the NPC cell line CNE-2. The group has reported the feasibility of using its metastasis model and cellular clones to identify novel molecules promoting tumor metastasis (Li et al., 2011a; Li et al., 2011b; Li et. al., 2012). So far, three molecules have been characterized as key elements in promoting NPC metastasis—serglycin, HSP27, and interleukin-8 (Li et al., 2011a; Li et al., 2011b; Li et. al., 2012). The researchers aim to validate at least two more key molecules, and all of these molecules could be targets for drugs to prevent and inhibit the systemic spread of cancer cells.

In terms of the soil, Dr. Qian and colleagues have found that before metastasis, a primary tumor can remodel the vasculature of the sentinel lymph node, preparing the mi-

croenvironment to better support the growth of the metastatic cancer cells that later arrive (Qian et al., 2006; Qian et al., 2007). The group has also shown that the key vasculature component that is remodeled is a special type of blood vessel called the high endothelial venule (HEV). It is speculated that remodeled HEVs not only promote the growth of metastatic cancers, but also facilitate the further spread of cancer cells to distant organs. This ongoing study aims to identify key molecules in the remodeling process of HEVs. The overall goal is to inhibit such remodeling and thus the spread of cancer cells from the sentinel lymph nodes.

Postponing cancer onset

Thanks to the development and application of new technologies, it is likely that in the near future we will be able to predict an individual's risk of cancer. However, the ability to predict risk raises an important clinical issue: how will we manage individuals at a high risk of a particular type of cancer?

Recently, Dr. Qian hypothesized that even though people harbor a genetic susceptibility to cancer from birth, there could be "postponing molecules" in the body that delay the onset of cancer (Qian et al., 2010). If this is correct, by amplifying the postponing mechanism we should be able to delay this onset and provide individuals with a longer cancer-free period. To test this novel hypothesis, Dr. Qian and his colleagues launched a pilot study using NPC as the disease model. By applying high-throughput screening of tumor and normal tissues from individuals of different ages, they have identified some candidate postponing molecules. Unexpectedly, they also found some "accelerator" candidates that appear to be related to early cancer onset. Animal models of carcinogenesis could be used to test both sets of candidate molecules. This is a typical translational study that aims to solve a clinical problem through a series of basic research approaches.

Dissecting tumor vasculature

Antiangiogenic therapy has provided unexpectedly limited survival benefits to cancer patients, and this has necessitated an examination of the complexity of tumor angiogenesis (Qian et al., 2009; Qin et al., 2012). Dr. Chaonan Qian and his colleagues were the first group to differentially analyze tumor vasculature in clear-cell renal-cell carcinoma using a molecular classification (Yao et al., 2007; Cao et al., 2012). An ongoing project of this group is identifying the cellular origin of the undifferentiated vessels. This study will open the possibility of more specific inhibition of tumor angiogenesis by targeting different types of tumor vasculature, thus enhancing therapeutic outcomes and improving patient survival. The strong connections among researchers studying kidney cancer at SYSUCC, the National Cancer Center Singapore, and the Cleveland Clinic in the United States led to a recently published study (Cao et al., 2012), and this will pave the way for additional successful collaborations in the future.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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